

EFFECTS OF INTRACEREBRAL AND SUBCUTANEOUS ADMINISTRATION OF TETANIC ANTI-TOXIN IN TETANUS AS OBSERVED IN NINE CASES.¹

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THE true value of the serum treatment of tetanus cannot be fairly established without the careful consideration of many cases candidly discussed.

The disease, as generally considered by surgeons, is rightly regarded as one of the most formidable maladies one has to treat, yet occasional writers rate the general mortality as low as 50 per cent. Under the best forms of treatment most writers, however, regard 80 per cent. as more nearly correct.

My own experience up to the last two years has been limited to six cases, extending over twenty-five years; of these only one recovered. During the last two summers nine cases have presented themselves for treatment at Roosevelt Hospital, under my care, and were subjected to serum treatment, with varying results, the reports and conclusions as to which I will briefly report.

I confess to have been rather sceptical as to the value of the subcutaneous method of serum treatment from reported cases, but was impressed by the novelty and promise of the treatment by intracerebral injections as outlined by Roux and Borrel. It is decidedly in the line of progress that our first promise of help should come from the laboratory; and the experimental use of injections into the brain in guinea-pigs,

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whereby Roux succeeded in saving thirty-five successive tetanized pigs out of forty-five thus injected, is an ample warrant for the employment of this method in the human subject. It is an eminent improvement over the subcutaneous method, which in the laboratory saved only two out of seventeen tetanized guinea-pigs.

In Roux and Borrel's article (*Annals of Pasteur Institute*, April, 1898) the position is taken that the poison of tetanus is fixed in the nerve tissue, notably in the brain-cells, which have a special affinity for the toxine, as in hydrophobia. The only satisfactory explanation of the better action of antitoxin by cerebral injection is based on these facts: that passive immunity in an animal which has received antitetanic serum injections, enables it to resist many times the fatal dose of toxin; it is thus resistant because of the circulating antitoxin in the blood; in a victim of traumatic tetanus, the toxine has already been taken out of the blood by the nerve-cells, and the injection of the antitoxin into the circulation meets and destroys merely that portion of the poison which is still in the blood, whilst the intracerebral injection infiltrates the cerebral tissue, and is believed to bring about an alternative action on the cells proper.

A few cases only have been reported of cerebral injection, a number insufficient to draw a final conclusion as to its value. Dr. Rambaux, of this city, collected nine cases from foreign journals reported up to December, 1899. (See *New York Medical Journal*, December 17, 1898.) I am able to add nine cases from my recent personal experience.

CASE I.—A. B., aged twenty-two years, was shot, July 3, 1898, in the left thigh. When he came to Roosevelt Hospital on the following day there was a wound of entrance but none of exit. Probing and radiograph failed to show a bullet. He left the hospital with a small sinus, to be treated in the Out-Patient Department. Sixteen days after the injury, July 19, he began to have dysphagia, trismus, and rapidly developing muscular stiffness. The wound became hardened and brawny. On the third day there developed convulsive spasms, opisthotonos, risus sardonicus, and general tonic spasms. The patient was brought back to the hospital with a temperature of 99.2° F., pulse 104. The wound was excised, a continuous bichloride dressing

applied, and twenty cubic centimetres of Board of Health antitetanic serum were subcutaneously administered. In addition, he received forty grammes of chloral, thirty grammes of bromide, and one-quarter grain of morphine.

The general spasms were somewhat lessened; he swallowed better, and had but few spasms during the next day. Then the wound was dressed with weak iodine solution; twenty cubic centimetres of antitoxin were administered three times subcutaneously, in addition to internal use of chloral 110 grains, one-quarter grain of morphine, bromide 220 grains. Temperature, 102.1° F.

On following day he had less spasm, and received again the same medication. Temperature rose to 102½° F. General spasm continued.

On the 25th he had passed a restless night; still fewer spasms; temperature, 104° F. Antitoxin omitted; continued bromide, chloral, and morphine.

July 26.—Fewer and milder spasms; trismus and opisthotonos continued; medication same. Maximum temperature, 103.2° F.

July 27.—Fewer spasms; comfortable night; one severe spasm in morning. Gave antitoxin twice, twenty cubic centimetres, and medication continued as before. Chloral, 100 grains; bromide, 180 grains; morphine, one-quarter grain. Temperature, 101° F.

July 28.—Had a number of severe spasms at night; became delirious at intervals during day; had involuntary micturition and defecation. Antitoxin, forty cubic centimetres. Temperature, 102.6° F.

July 29.—Spasms continued; patient losing ground; delirious. Stopped antitoxin. Maximum temperature, 105° F.

July 30.—Delirium continued. No nourishment taken. Temperature, 106.4° F. Death in spasm.

This case showed progressive exhaustion from continued chronic and tonic spasms, inability to nourish, and general toxæmia, although nourishment was given by tube and rectum. The antitoxin seemed at first to have some control of spasm, but failed afterwards to show an appreciable value.

CASE II.—P. F., aged sixteen years. October 4, 1898, ran a nail into the sole of his left foot. The wound was incised and packed in Out-Patient Department.

October 10.—Sixth day. Lockjaw set in, with opisthotonos of the back of the neck. Wound found indurated; temperature, 101° F.

Wound excised ; cavity packed with weak iodine gauze ; given twenty cubic centimetres antitoxin subcutaneously ; chloral, fifteen grains ; bromide, thirty grains.

October 11.—Slight increase of stiffness in arms and neck ; 100 cubic centimetres of antitoxin during day ; morphine, one-quarter grain ; chloral, eighty grains ; bromide, 240 grains ; nutritive enemata. Temperature, 104.2° F. Muscular spasms continued to increase from first rapidly. Patient had numerous slight convulsions during night, and died October 12, in violent convulsion, which lasted five minutes, seeming to arrest respiration beyond control.

This case seems to indicate the inefficiency of serum furnished by the Board of Health, used subcutaneously and in moderate quantity in a grave case.

CASE III.—P. McL., aged eight years, was shot July 4, 1899, by a toy-pistol in the left forefinger, and the wound was dressed at a drug store.

July 9 he complained of difficulty in swallowing, and awoke in the morning with head thrown back and jaws locked.

July 10 he was admitted to the Roosevelt Hospital, with cramps in back, progressive stiffening of neck and jaws ; muscles of neck and back and abdomen were found rigid ; skin bathed in perspiration ; frequent spasm of back and spinal muscles, dyspnoea ; temperature, 100.8° F. The hand was dressed. Chloral, twenty grains, bromide, forty grains, were given every three hours ; temperature, 101° F. On the following morning was given twenty cubic centimetres of antitoxin (Board of Health) ; opisthotonos and general spasm, with cyanotic dyspnoea ; temperature, 105.2° F. ; respiration, 40. During the day the spasms were so incessant that he became rapidly exhausted, and died in the afternoon of the next day, July 11, in a respiratory spasm.

CASE IV.—W. R., aged nine years, received, July 4, 1899, a toy-pistol wound in the centre of his left palm.

July 11 his jaws became stiff and sore.

July 12 he entered hospital with pronounced lock-jaw, rigidity of muscles of neck, back, and injured arm ; flexor spasms of forearm of left hand ; difficulty in swallowing ; temperature, 100° F.

I directed my assistant, Dr. Fisk, to make an intracerebral injection of tetanus antitoxin, which was done at the back of the fissure of Rolando, two inches from the median line. The needle was pushed one inch into the brain substance, introducing three cubic centimetres

on each side. Twenty cubic centimetres were also given subcutaneously. Chloral, ten grains, bromide, twenty grains, were given at intervals of three hours, per rectum. The tetanic spasms continued during the following day with increased spasm of injured arm. Sixteen hours after first cerebral injection a second was given, the needle being plunged through the trephine wound. The subcutaneous use of the antitoxin was continued every six hours, twenty cubic centimetres; no marked improvement was apparent up to the end of forty-eight hours, but rather increase of general muscular rigidity. The Parke-Davis antitoxin was begun on the 14th, owing to the Board of Health supply having given out; ten cubic centimetres were given three times daily during July 14 and 15.

July 15 he slept a good part of the night without spasms, and was very quiet. The antitoxin was given five times on the 16th; nutritive enemata; application of ice to the nape of the neck on account of severe pain from muscular spasms; an occasional small hypodermic of morphine; dressing of wound under chloroform. This constituted the treatment for a number of days. The patient, up to the fifth day, presented all the profound symptoms of tetanus; was excited to spasms by handling abdomen. Intense spasm of hand and forearm muscles, relieved by immersion in warm bath of bichloride, 1-10,000. On the fifth day of treatment a dark erythematous rash appeared on the upper half of the left arm and other parts of the body, such as frequently occurs in the administration of antitoxines. Lockjaw was still complete and absolute. There were occasional spasms on this day.

Seventh day, antitoxin, ten cubic centimetres, four times; extreme opisthotonos and general spasms frequent during the day.

Eighth day, rash disappearing.

Ninth day, antitoxin serum, ten cubic centimetres, five times; wounds dressed with peroxide of hydrogen; spasms milder.

Tenth day, passed through morning without spasms.

Thirteenth day, improvement in jaws, which showed slight relaxation. Had been receiving up to this day from fifty to sixty cubic centimetres of antitoxin daily. To-day, fever set in, and consolidation of upper right lobe of lung appeared. Given nitroglycerin; serum continued to the extent of forty cubic centimetres daily; temperature, 105° F. Some increase of muscular rigidity, patient showing exhaustion. Following day, temperature, 105° F. Given nitroglycerin ($\frac{1}{100}$ grain), six times, with strychnine.

Sixteenth day, muscular rigidity much diminished ; temperature, 105.2° F.

Seventeenth day, rigidity and spasms almost gone ; fever less ; opens mouth one-half inch ; little delirious ; oxygen and various stimulants given.

Nineteenth day, more improvement shown ; slept naturally ; pneumonia resolving. During next few days pneumonia cleared, temperature fell, and spasms disappeared, except in the injured hand. Convalescence progressed favorably thereafter, with ultimate perfect recovery ; spasmodic contraction of hand remaining for about six weeks

CASE V.—L. H., aged eleven years, was shot in the left palm by a toy-pistol, July 5, 1899.

Eighth day had stiffness and soreness of muscles of lower jaw. On examination, same day, his jaw opened one-half an inch ; abdominal muscles were not stiff ; some pain in back, none in neck ; some stiffness of left wrist ; temperature, 100.2° F. On the afternoon of this day three cubic centimetres of Board of Health antitoxin were injected into anterior lobe of brain in an effort to place it in the ventricle, the point being located by the kindness of Dr. Rambeau ; at the same time twenty cubic centimetres were injected into the right pectoral region ; chloral and bromide also administered as usual.

Ninth day, tetanic symptoms much more marked ; patient had general muscular spasms, some sensory hyperæsthesia, special flexor spasms of hand and forearm of injured side ; increased knee-jerk in left lower extremity ; head thrown back. Later in the day dysphagia, frequent general spasms. Seventeen cubic centimetres of Board of Health antitoxin and twenty cubic centimetres of Parke-Davis antitoxin were injected.

Tenth day delirium set in ; dense muscular rigidity ; general spasms ; cyanosis from spasm of respiratory muscles. Patient showed rapid exhaustion ; went into opisthotonos on slight provocation ; dyspnœa severe ; death.

This case was one of the severe type ; though taken promptly, it showed no benefit from operation. Injection of Board of Health serum at first was used, and later this was supplemented by a single injection of Parke-Davis antitoxin, but too late to be credited.

CASE VI.—J. M., aged eleven years, was admitted, July 15, with a Fourth of July toy-pistol wound in the centre of his left palm, part

of the wad having been retained. On admission there was some rigidity of the muscles of forearm and hand, which were in a condition of partial flexion, extending up to the elbow-joint.

The case seeming to be of a milder type, I thought it best not to subject the serum treatment to test unless severer symptoms set in.

For one week the muscular rigidity was confined to arm and pectoral region, the only medication being wound treatment with peroxide of hydrogen, and immersion of arm in a hot, weak bichloride solution (1-10,000).

During the second week, from eighth to thirteenth days, slight lockjaw symptoms set in, with general muscular rigidity, but no spasms.

Chloral and bromide were given with no apparent effect. On the fifteenth day after admission general stiffness of all the muscular system became more pronounced, extending to the upper and lower extremities, and the case began to assume a serious aspect.

Two pronounced general spasms with opisthotonos occurred within a few hours. Thirty cubic centimetres of antitoxin serum (Parke, Davis & Company) were given subcutaneously, and continued at fifty cubic centimetres daily for one week.

During this week there was gradual and continuous improvement, there seeming to be a very positive evidence of change from unfavorable to favorable progress.

For three days the serum injections were omitted, during which time there was an arrest in the improvement of the muscular rigidity; he became restless, irritable, did not sleep, the legs and abdominal muscles remaining stiff. Parke, Davis & Company's serum, ten cubic centimetres every four hours, was again given, and patient made continuous improvement, continuing serum in small doses until the fourth week. Good recovery.

This case, though representing a milder type, was arrested at its progressive stage by the Parke, Davis & Company's serum, given hypodermically, and retrograded slightly on stopping medication; improvement being resumed when it was again administered.

CASE VII.—J. B., aged fifteen years, sustained a toy-pistol wound of the right hip, in the gluteal fold, July 4, 1899.

On the ninth day, July 13, stiffness of the jaw set in, followed by

oppression of the chest, and by stiff neck and back. In a few hours he had lockjaw, respiratory spasm, and one severe general spasm, with opisthotonos.

On admission, July 18, risus sardonicus was well marked. The jaw was firmly closed, the abdomen, neck, and back were rigid; also the right knee and hip-joint, this being the injured side. The hamstring tendons were tense and the leg could not be brought straight. General hyperæsthesia and increased knee-jerk were present.

The gluteal wound was two inches deep, and about it a marked hard œdema, like lardaceous infiltration, was present. This was promptly excised under chloroform, and peroxide applied.

Later in the afternoon, July 18, I made a double cerebral injection of antitoxin (Parke, Davis & Company), three cubic centimetres, in each frontal lobe.

Cocaine anaesthesia only was used, and no difficulty whatever experienced, the skin alone needing cocaine. The smallest trephine was used, one-quarter-inch diameter, through a one-inch incision made at Roux's point, half-way between the outer angle of the orbit and a point in the vertex, at the junction of the line crossing over between the two auditory canals. No sensation was noted by the patient during the cerebral injection, nor was there any effect produced upon pulse or respiration.

The needle was carried two inches deep into the brain substance. Antitetanic serum (Parke, Davis & Company), ten cubic centimetres, was given also every four hours, subcutaneously.

Two hours after the cerebral injection in this case it was already noticed that the risus sardonicus was less marked, and that the rigidity of the muscles of the neck, jaw, and abdomen had abated a little. The patient also expressed himself as feeling more comfortable.

On the following day the tendency to spasm was less, although stroking the abdomen would bring on opisthotonos. The leg continued very stiff.

During the following week the general muscular rigidity of jaws, face, neck, and back abated a very slight but appreciable amount each day, the patient receiving fifty cubic centimetres (Parke, Davis & Company) daily, in addition to a moderate amount of chloral and bromide. Slight rise of temperature, one degree, on two occasions to 101.5° F., was relieved at once by calomel purge, but at the expense of a slight stomatitis at the end of a week. An urticarial rash appeared on the thighs, forearms, and back on the tenth day after

serum treatment, which, however, disappeared in two days in spite of its continued use.

On the tenth day after the operation there was rapid improvement in the rigidity, and his general appearance was much better.

By the twelfth day the risus sardonicus had disappeared, the jaws could open seven-eighths of an inch, rigidity of abdomen, back, and neck had largely disappeared, so that the chin could be brought down to touch the sternum. On the fourteenth day the serum treatment was stopped.

Four days later nothing remained but a little rigidity of right leg.

This case illustrated rather strikingly slight improvement at once after treatment, and complete arrest of rapidly progressing tetanus, the disease beginning on ninth day after injury, and promising to be of a severe type unless arrested by treatment. It was of interest to note that the trephining was easily done by aid of cocaine.

CASE VIII.—T. B., aged fourteen years, on July 24, 1899, sustained a wound of the left index finger by a toy-pistol shot. On the sixth day thereafter lockjaw symptoms set in; first in the jaw, extending in twenty-four hours to neck, back, and injured arm. The opisthotonos spasms occurred every ten minutes during this day; on the following day, August 11, he was admitted to hospital (eighteen days after injury, and second day of disease).

He was a healthy looking boy; temperature, 99.6° F.; pulse, 100; respiration, 28; jaws were fixed, but teeth could be separated about one-fourth of an inch; face showed marked risus sardonicus; neck and back were very rigid; moderate sensory hyperæsthesia; no exaggeration of reflexes; frequent general muscular spasms took place on slight provocation, with marked opisthotonos.

At 5 P.M., an intracerebral injection of Parke, Davis & Company's antitoxin, four cubic centimetres on each side, was done under chloroform; the needle was introduced one and three-fourths inches into the brain. Antitoxin, twenty cubic centimetres, was also injected subcutaneously, and later ten cubic centimetres every four hours. Chloral and bromide were given every four hours. Violent spasms occurred every one-half or three-quarters of an hour. The patient was regarded as in an extremely dangerous condition; during the next twenty-four hours these spasms were not perceptibly affected, occur-

ring at intervals of one-half to one hour. About ten hours after operation, the patient went five hours without a spasm, but later extreme irritability was present, the slightest touch causing opisthotonic spasms. Two morphine hypodermics were given to dull the irritability. During the second twenty-four hours he evinced difficulty in swallowing, spasms continued hourly. Temperature continually rose till it reached 106° F.; respiration, 140, at 9 P.M. Cold sponging was given with relief, temperature fell to 104° F., and patient fell asleep for three hours. Serum was given subcutaneously to the amount of eighty cubic centimetres in the twenty-four hours. During the latter half of the second day, the disease progressed in spite of the antitoxin. During spasm, the muscles seemed to be universally rigid; marked cyanosis would intervene; oxygen was given and chloroform as needed, camphor, digitalis, etc., used, but spasms increased, and patient died, without abatement of disease, thirty-six hours after the intracerebral injection, with a temperature of 107° F.

This case presented no appreciable benefit from the antitoxin treatment, but must be classed as one of the gravest types of the disease brought under care at a late stage.

CASE IX.—M. S., aged eight years, on September 6, 1899, stepped on a nail, making a punctured wound in the sole of his right foot, which made him walk a little lame for two weeks, so that he noticed no special muscular stiffness till September 25 (nineteenth day after accident), when he commenced to have pain in the small of his back, with stiffness of his jaw and the right leg. This increased and extended to other parts of his body until his admission to Roosevelt Hospital, September 27, on the twenty-first day after injury.

Examination showed muscular rigidity, affecting the muscles of back, abdomen, and neck and lower extremities; most marked in the injured leg. The thigh, leg, knee, and ankle were fully extended; the toes stiffly extended in a straight line; the foot rigidly held in extreme talipes equino-varus; the jaws could be separated one-fourth of an inch; slight risus sardonicus; temperature, 101° F.

Ten cubic centimetres of antitetanic serum (Parke, Davis & Company) were given every six hours. The disease having begun after three weeks' incubation, the case was regarded as one which might continue of a milder type and be credited with a cure by the old-fashioned treatment. It was therefore decided to wait and watch the

patient until the development of graver symptoms, before testing the intracerebral injection.

After twenty-four hours, the rigidity of the jaw had increased, so that voluntary separation of the teeth was impossible; there was increase also in the muscular rigidity of the right leg, back, neck, and abdomen. Risus sardonicus was also more marked, and there was more sensory hyperæsthesia.

Two general spasms occurred; boy refused nourishment on account of difficulty in swallowing, and was fed by nutritive enemata.

Trephining and intracerebral injection of Parke, Davis & Company's serum was done under chloroform, September 28 (twenty-second day since accident), third day of disease.

The needle was introduced one and one-half inches and six cubic centimetres injected into the brain, one-half on each side. During the following twenty-four hours the maximum temperature was 100.2° F.; ten minims of antitoxin were injected subcutaneously every six hours. There was no change during the twenty-four hours in muscular rigidity, although he slept better and had no spasms. During the next day, temperature, 101° F., fifty cubic centimetres of serum were injected; bromide was also given. He slept well; the muscular condition was stationary, except that the chin could be brought a little closer to the sternum; no spasms; rash appeared on nose and forehead and chest; temperature, 100.5° F.

October 1.—Third day. Showed great improvement; has slept well; the general muscular rigidity was decidedly lessened; no spasms; jaw could be opened three-eighths of an inch; serum continued, fifty cubic centimetres; with bromide; temperature, 100.4° F.

October 2.—Fourth day. Still improving in muscular rigidity; jaws relaxed one-half inch; slept well; took nourishment; temperature, 100.8° F., fifty cubic centimetres serum, bromide.

October 3.—Fifth day. Omitted serum; risus sardonicus disappeared; jaws relaxed three-fourths of an inch; no rigidity of neck or arms; abdominal rigidity very slight; foot still held in equinovarus; the muscles of the calf, which had been continuously contracted and stood out as hard as wood, were now softening; maximum temperature, 100° F.

October 4.—Sixth day. Little rigidity left anywhere, but in right hip and ankle. Sat up in bed ninth day. Urticarial rash on legs, trunk, arms, and face; temperature, 100° F.; boy seemingly otherwise well.

October 11.—Rash had disappeared on October 10, tenth day;

temperature normal. Sat up in chair; went out in garden on the fourteenth day. Three weeks after operation went home, slight rigidity of ankle still remaining.

Remarks.—Considering the foregoing cases, I would note that the common observation that a long period of incubation is an absolute criterion of the probable severity is an error.

In considering these nine cases, I find two only can be regarded as in sense of a milder type, one commencing on the 10th, and one on the 19th, the day after injury. The other seven were of a grave type.

Of the seven occurring during the epidemic of the past summer, five were so severe, either at the onset or in the progress of the disease, that they were deemed worthy of being subjected to the test of trephining. Of these five, three recovered and two died.

The cases which recovered had their onset on the seventh, ninth, and nineteenth day of incubation; the cases which died, on the eighth and sixteenth day of incubation.

In two of the trephined cases the Board of Health toxine was used; one died and one recovered. In three cases Parke, Davis & Company's serum was used; two recovered and one died.

There were five of the nine cases in which one could perceive an apparent effect of the serum treatment.

In Case No. I, in which it was given only subcutaneously, the Board of Health serum (1898) was used (see note). Though the patient subsequently died, improvement was certainly noticed.

In Case No. IV, Board of Health serum (1899) was used by trephine and subcutaneously, and the patient recovered.

In Case No. VI, the Parke, Davis & Company serum was used only subcutaneously. Improvement was demonstrated, and the patient recovered.

In Cases Nos. VII and VIII the Parke, Davis & Company serum was used, and the favorable effect was observed. Both were trephined and serum used in the brain and subcutaneously. Both recovered.

The favorable action was shown either in a prompt arrest of the general convulsive spasm or in an abatement of the progressively bad symptoms.

The serum furnished by Parke, Davis & Company was available in the midst of the summer epidemic of tetanus, if we may call it so, at the moment when the Board of Health ceased to furnish more from lack of supply, and it proved itself, both by comparison and in its actual results, noticeably more efficient.

This limited experience leads me to regard it as a valuable adjunct in the scientific treatment of this grave malady, and I can but regard the cerebral injection as an advance over the subcutaneous method worthy of extended trial and further study.